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Development of polypoidal lesions in age-related macular degeneration

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Abstract

Purpose To investigate the development of polypoidal lesions using indocyanine green angiography (IA) in eyes with typical age-related macular degeneration (AMD).

Methods We reviewed retrospectively the medical records of 47 consecutive patients (47 eyes) with typical AMD who had been followed-up with IA for at least 2 years.

Results At the initial visit, while all eyes showed classic and/or occult choroidal neovascularization (CNV) associated with AMD, no eyes showed polypoidal lesions by IA. During the follow-up, however, 13 (27.7%) of the 47 eyes did show polypoidal lesions. All polypoidal lesions developed at the edge of persistent CNV or, more often, at the terminus of recently progressed CNV. Of 12 eyes with a final lesion area of > 8 disc area, 7 (58.3%) showed newly developed polypoidal lesions. In eyes with these newly developed polypoidal lesions, the mean area of the vascular lesion had extended significantly from 10.50 ± 7.88 mm^2 to 20.87 ± 10.21 mm^2 during the follow-up (P = 0.0018).

Conclusions The current observation suggests that IA of active AMD sometimes reveals polypoidal lesions if there is progression of the CNV in the sub-retinal pigment epithelium space.

Keywords: age-related macular degeneration; indocyanine green angiography; polypoidal choroidal vasculopathy

Introduction

Initially, polypoidal choroidal vasculopathy (PCV) was described as a new clinical entity with a unique form of choroidal vascular abnormality.[1-3] Since Uyama *et al*[4, 5] proposed that PCV is a variant of choroidal neovascularisation (CNV) in exudative age-related macular degeneration (AMD), it has been generally believed that the vascular components in PCV are a type of CNV, although the pathogenesis of PCV is not fully understood.[6, 7] In general, PCV is diagnosed when polypoidal lesions are seen by indocyanine green angiography (IA) at the terminus of typical branching vascular networks.[8] IA is essential for the study of the vascular lesion of PCV because most of the vascular components of PCV are located beneath the retinal pigment epithelium,[8] so with fundus examination or fluorescein angiography (FA), it is often difficult to distinguish macular PCV from exudative AMD.[9-11]

An increasing number of reports have recently shown that anti-vascular endothelial growth factor (VEGF) therapy can reduce the exudative change and lesion size in exudative AMD, and can result in visual recovery.[12-18] However, some eyes with exudative AMD are refractory to repeated anti-VEGF therapy.[19, 20] Clinicians sometimes see cases of typical AMD with a large lesion that shows a poor response to treatment and that shows progression, which results in a poor visual prognosis. When we performed IA on such AMD cases with large lesions, we sometimes noted knob-like hyperfluorescent lesions at the end of progressing CNV, which resembled the polypoid lesions typically seen in PCV.[21] Cho *et al*[19] reported that IA revealed

these polypoidal lesions in 12 cases of exudative AMD with a poor response to anti-VEGF therapy.

In the clinical setting, FA is essential to make a diagnosis and to evaluate lesion size and its activity in exudative AMD.[22] Even in exudative AMD, IA often provides useful information about the vascular lesions, especially those located beneath the retinal pigment epithelium.[23, 24] So far, however, limited information is available using IA on long-term observations of the vascular components in typical AMD. In the study described herein, we studied the vascular lesions of typical AMD with the use of IA, in order to elucidate the rate and characteristics of eyes that were initially diagnosed as having typical AMD and that subsequently developed polypoidal lesions.

Patients and methods

For this observational case study, we reviewed retrospectively the medical records of 47 consecutive patients (47 eyes) with typical AMD who initially visited the Macula Service, Department of Ophthalmology, Kyoto University Hospital between October 2004 and October 2007 and whose eyes had been examined with both FA and IA for more than 2 years after the initial visit. During this period, 116 patients with typical AMD initially visited our clinic. Sixty-nine patients were excluded from the current study because of a short follow-up period or because they lacked FA or IA during the more than 2 years since the initial visit. When both eyes showed typical AMD, only one eye was selected randomly for inclusion in the current study. This study was approved by the Institutional Review Board at Kyoto University Graduate School of Medicine and adhered to the tenets of the Declaration of Helsinki.

The diagnosis of typical AMD was based on fundus photographs, FA, IA and optical coherence tomography (OCT), which showed type 1 and/or type 2 CNV. Eyes with other macular abnormalities (i.e., PCV, retinal angiomatous proliferation, pathologic myopia, idiopathic CNV, presumed ocular histoplasmosis, angioid streaks, and other secondary CNV) were excluded from the current study. When reddish-orange nodules were seen by ophthalmoscopic examination or polypoidal lesions were seen by IA, the eye was excluded from the current study. Eyes that had been treated previously with focal laser photocoagulation, photodynamic therapy, vitrectomy, radiation therapy, or anti-VEGF therapy were also excluded from the

present study.

At the initial visit, all patients had undergone a comprehensive ophthalmologic examination, including measurement of best-corrected visual acuity (VA), determination of intraocular pressure, indirect ophthalmoscopy, slitlamp biomicroscopy with a contact lens, and OCT. After fundus photographs were taken, FA and IA were performed on each patient using a confocal laser scanning system (HRA-2, Heidelberg Engineering, Dossenheim, Germany). VA measurement and OCT examination were performed on each patient at each follow-up visit; FA and IA were performed if necessary, and all patients in the current study were examined with both FA and IA several times during their follow-up.

In this study, greatest linear dimension (GLD) and area of the lesion were determined based on the IA with software that was built into the HRA-2. GLD was defined as covering the entire CNV lesion, including type-1 and type-2 CNV, polypoidal lesions, and the branching vascular network. Area of the CNV lesion was measured manually with software in the HRA-2. The pigment epithelial detachment, without underlying CNV, was not included in measurement of the GLD or in area of the lesion. In the current study, one optic disc area (DA) is considered to be 2.54 mm^2 on the basis of one optic disc diameter being 1.8 mm.

Using OCT images, we performed two measurements with a caliper that was built into the software of the OCT machine; using these calipers, foveal thickness and thickness of the neurosensory retina in the fovea were measured. Foveal thickness was defined as the distance between the vitreoretinal interface and the retinal pigment

epithelium; thickness of the neurosensory retina was defined as the distance between the vitreoretinal interface and the tip of the outer portion of the inner and outer segments of the photoreceptors.

In the current study, measurement values obtained at the initial visit were compared with those obtained at the final examination. To evaluate progression of the vascular lesions, the initial area of the CNV lesion and of the GLD were compared with final values. To evaluate activity of the disease, we also compared the initial OCT measurement (foveal thickness and thickness of the neurosensory retina) with values obtained at the final visit. To compare the difference in VA, vision as measured with a Landolt chart was converted to a logarithm of the minimal angle of resolution (logMAR).

Statistical analysis was performed using software designed for this purpose (StatView, version 5.0; SAS Institute, Cary, North Carolina, USA). A *P* value of less than 0.05 was considered to be statistically significant.

Results

In the current study, 47 eyes of 47 patients (36 men and 11 women) with typical AMD were examined; the patients ranged in age from 56 to 90 years (72.8 ± 7.5 years). The follow-up period ranged from 24 to 59 months (43.9 ± 10.3 months). All patients were examined with FA and IA repeatedly during their follow-up, ranging from 2 to 10 times (4.6 ± 1.8 times). Table 1 shows characteristics of patients who were eligible for this study. Mean baseline VA (logMAR) was 0.70 ± 0.53, and mean initial area of the lesion and GLD were 8.68 ± 7.75 mm^2 and 3850 ± 1627 μm, respectively. Figure 1 shows the relationship of area of the lesion and of the GLD obtained at the initial visit and at final examination. The initial area of the lesion (R = 0.7347, $P < 0.0001$) and initial GLD (R = 0.7349, $P < 0.0001$) were correlated closely with final values.

At the initial visit, although all eyes of the patients involved showed classic and/or occult CNV associated with AMD, no eyes showed polypoidal lesions by IA. During the follow-up period, 34 eyes were initially treated with photodynamic therapy, and 5 were initially treated with anti-VEGF therapy. In spite of these treatments, however, some eyes with typical AMD showed extension of the vascular components with an exudative change. The mean area of the neovascularisation increased from 8.68 ± 7.75 mm^2 to 14.28 ± 10.57 mm^2 during follow-up ($P < 0.0001$). Also during the follow-up, 13 (27.7%) of the 47 eyes showed polypoidal lesions by IA. All of these polypoidal lesions developed either at the edge of persistent CNV (Figure 2) or, more often, at the terminus of the newly progressed CNV (Figures 3 and 4). Of 12

eyes with a final CNV area of > 8 DA, 7 (58.3%) showed newly developed polypoidal lesions (Figure 1).

Depending on the development of polypoidal lesions, we divided our patients with typical AMD into two groups—those with polypoidal lesions (n = 13) and those without polypoidal lesions (n = 34). Table 1 shows baseline and final measurement values of each group. There were no significant differences in gender or age between these two groups (P = 0.9739 and P = 0.8913). Furthermore, there were no differences in VA (P = 0.6234), area of lesion (P = 0.3262), or GLD (P = 0.3269) at the initial visit. Mean area of the lesion in eyes with polypoidal lesions enlarged significantly from 10.50 ± 7.88 mm^2 to 20.87 ± 10.21 mm^2 during the follow-up (P = 0.0018). Mean GLD in eyes with polypoidal lesions also progressed significantly from 4231 ± 1692 μm to 5880 ± 1947 μm (P = 0.0032). Although mean area of the lesion and GLD were increased in eyes without polypoidal lesions, the increases were significantly greater in eyes that developed polypoidal lesions (P = 0.0036 and P = 0.0035). In eyes with polypoidal lesions, however, final VA was not statistically different compared with that in eyes without polypoidal lesions (P = 0.2303).

Discussion

PCV was first described as a new clinical entity with an associated unique form of choroidal vascular abnormality.[1-3] Subsequently, however, based on histologic specimens and OCT examinations, PCV is thought to be a unique form of CNV.[25, 26] In general, presumed exudative AMD is diagnosed as PCV when IA shows polypoidal lesions at the terminus of the branching vascular network.[8] In PCV, IA is essential to make the diagnosis and to evaluate precisely the entire vascular lesion.[8] In the current study, polypoidal lesions developed in 27.7% of eyes with typical AMD—eyes that had shown no polypoidal lesions at the initial visit. All polypoidal lesions developed at the edge of persistent CNV or, more often, at the terminus of recently progressed CNV. The current observation suggests that active AMD may show polypoidal lesions, if there is progression in the sub-retinal pigment epithelium space.

The tip of the extending CNV, which is the most active lesion, typically shows vigorous leakage on FA.[22] Even if the CNV is located beneath the retinal pigment epithelium, it sometimes shows a ‘classic’ appearance, as proposed in the updated clinicopathologic classification of subretinal neovascularisation by Gass.[27] Because molecules of indocyanine green readily attach to serum albumin,[28] vigorous leakage is not seen usually by IA, even from active CNV,[23, 24, 29] but CNV that is stained by indocyanine green may well appear as knobbed hyperfluorescent spots on IA.[30] In our patients, the tips of progressive CNV associated with AMD that showed focal hyperfluorescence on IA might appear to be polypoidal lesions.

Another interpretation is also possible. We can assume that the branching vascular network and polypoidal lesions represent a variant of type-1 CNV associated with exudative AMD.[4, 5] In the clinical setting, when no polypoidal lesions are seen, it is difficult to distinguish the branching vascular network from the type-1 CNV that may be associated with AMD.[31] Clinically, some polypoidal lesions do regress spontaneously or, more commonly, after photodynamic therapy, but they tend to recur at the same location or at other terminals of the branching vascular network.[6, 9, 32] In the current study, a diagnosis of typical AMD was made in all eyes, based on the initial IA. It is possible that some of our patients actually had PCV which was misdiagnosed, and that some showed polypoidal lesions during the follow-up. Recently, Maruko *et al*[33] reported that among 349 patients with neovascular AMD, 20 (5.7%) had one eye with PCV while the fellow eye showed typical AMD, but that PCV developed during the follow-up in ten eyes that had typical AMD at the initial examination. Because their patients had PCV lesions in the fellow eye, it is reasonable to assume that these eyes originally had PCV but did not meet the diagnostic criteria of PCV.[33]

Our patients had been examined with both FA and IA for more than 2 years after the initial visit. In the current study, the rate of those eyes that were refractory to treatment or that showed a recurrence of CNV after the successful initial treatment might be relatively high. Recently, Cho *et al*[19] reported that polypoidal lesions were detected in 12 cases of exudative AMD with a poor response to anti-VEGF therapy. In their report, treatment with photodynamic therapy, photodynamic

therapy/anti-VEGF combination therapy, or continued anti-VEGF monotherapy resulted in complete resolution of exudation in 9 of 12 eyes. In the current study, we showed that typical AMD refractory to treatment sometimes developed polypoidal lesions at the terminus of the newly progressed CNV. However, visual prognosis of these eyes was not poor. We treated eyes with polypoidal lesions primarily by photodynamic therapy or photodynamic therapy combined with ant-VEGF therapy. Today, anti-VEGF therapy is a primary treatment for typical AMD. In eyes with exudative AMD refractory to treatment, however, we suggest that clinicians should reconsider the treatment strategy after re-evaluation of the CNV by IA.

It is still controversial as to whether PCV is a distinct clinical entity or is simply a unique form of exudative AMD.[6] In Asian populations, a number of reports have shown that genetic variations in ARMS2 and CFH are associated strongly with both AMD and PCV.[34-38] In addition, Lima *et al*[39] recently reported that the PCV phenotype in Caucasian patients is associated with the three major AMD-associated loci, including CFH, ARMS2, and CFB/C2 genes, and they suggested that PCV and AMD are genetically similar in these tested loci.[39] While Kondo *et al*[40] have implicated the elastin gene as a susceptibility gene for PCV, it is generally thought that PCV and AMD share common genetic backgrounds, even though complications, treatment effect, and visual prognosis are somewhat different.[6, 11] Indeed, PCV is a distinct clinical entity,[9] although some advanced AMD cases do show features characteristic of PCV.[33]

Limitations of the current study are its retrospective nature and the various

treatment regimens used. In the current study, active AMD sometimes showed polypoidal lesions at the terminus of the vascular lesion, when the neovascularisation showed progression in the sub-retinal pigment epithelium space. In the clinical setting, eyes with a small PCV lesion often maintain good VA for a protracted period of time.[41, 42] In contrast, cases of PCV with a large lesion that has a poor response to treatment and that shows progression, tend to have a poor visual prognosis.[21] Our findings suggest that advanced AMD overlaps with PCV—at least with PCV that has a large vascular lesion.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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Figure legends

Figure 1 (a) Correlation between initial and final areas of the lesion in eyes with typical age-related macular degeneration. Initial areas are correlated significantly with final areas of the lesion (R = 0.7347, $P < 0.0001$). (b) Correlation between initial and final greatest linear dimension (GLD) in eyes with typical age-related macular degeneration. Initial GLD is correlated significantly with final GLD (R = 0.7349, $P < 0.0001$). One disc area (DA) is estimated to be 2.54 mm^2 on the basis of one optic disc diameter being 1.8 mm. Open diamonds represent eyes without polypoidal lesions and closed diamonds represent eyes with polypoidal lesions.

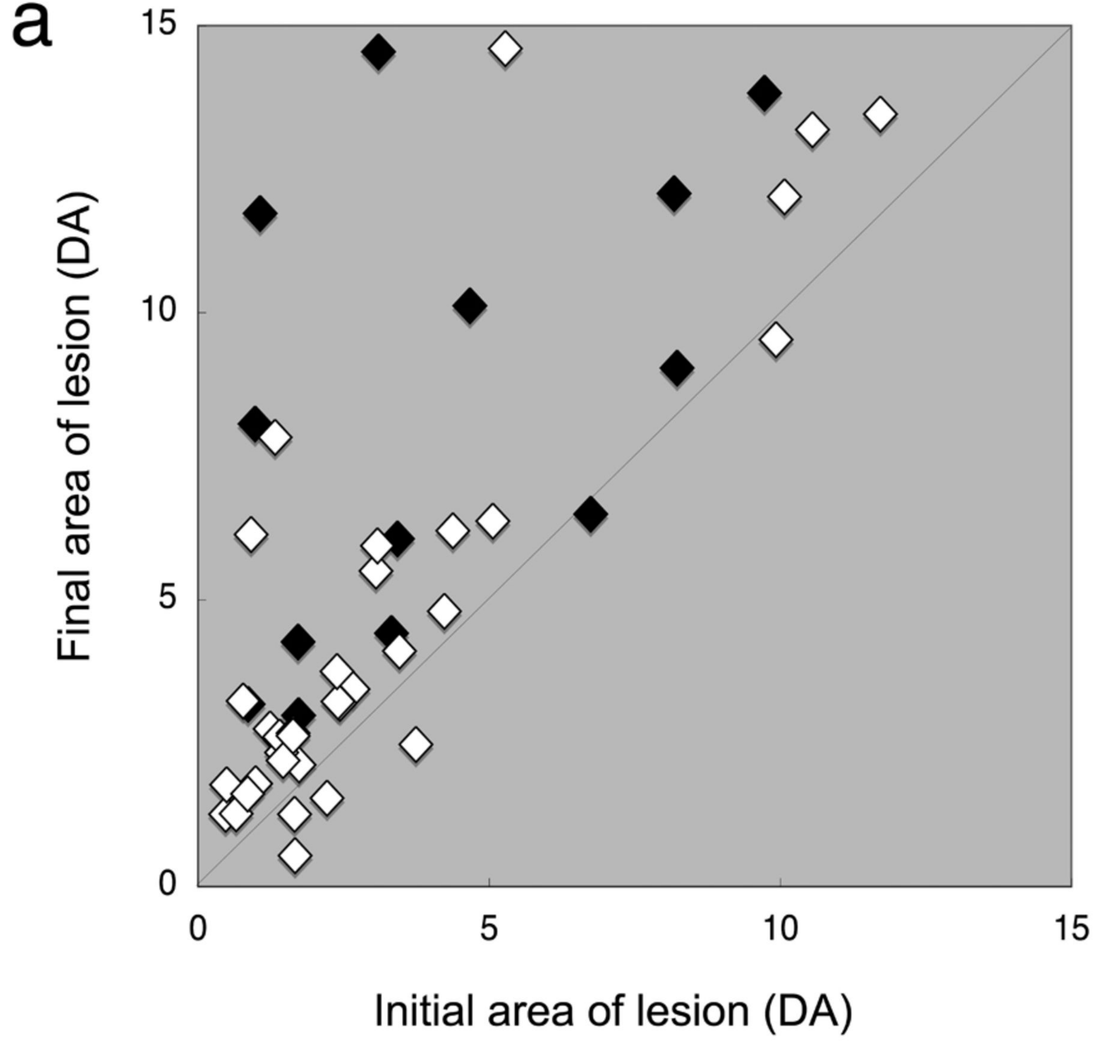
Figure 2 Development of polypoidal lesions at the border of persistent choroidal neovascularization (CNV) in a right eye with typical age-related macular degeneration. (a) Fundus photograph at the initial visit shows a multi-lobed serous pigment epithelial detachment (PED). Visual acuity was 0.8 in this eye. (b) Fluorescein angiography (FA) at the initial visit shows only hyperfluorescent areas associated with the PED. (c) Indocyanine green angiography (IA) shows CNV (arrow) at the edge of the PED; no polypoidal lesions are seen. (d) Fundus photograph at 34 months after the initial visit. With two photodynamic treatments, activity of the CNV has regressed. Visual acuity was now 0.2 in the right eye. (e) At 50 months after the initial visit, new serosanguineous PEDs (arrows) have developed at the upper side and inferotemporal side of the subfoveal disciform scar. (f) IA shows multiple polypoidal

lesions (arrows) at the edge of the persistent CNV. Visual acuity was 0.1 in this eye.

Figure 3 Development of polypoidal lesions at the terminus of newly progressed choroidal neovascularization (CNV) in a left eye with typical age-related macular degeneration. (a) Fundus photograph at the initial visit; at which time visual acuity in this eye was 1.2. (b) Fluorescein angiography (FA) at the initial visit shows inactive occult CNV. (c) Indocyanine green angiography (IA) shows no polypoidal lesions. (d) At 34 months after the initial visit, visual acuity had decreased to 0.15. Fundus photograph shows an active exudative change at the temporal side of a subfoveal disciform scar. (e) FA shows large subfoveal classic CNV with temporal active leakage from the CNV (arrow). (f) IA shows mature subfoveal CNV (long arrow). The CNV has progressed temporally and now forms multiple terminal bulbs, which are seen as polypoidal lesions (arrow). Three intravitreal injections of bevacizumab caused activity of the CNV to regress. (g) At 64 months after the initial visit, a new active lesion has developed on the upper border of the subfoveal disciform scar. Visual acuity, however, remained at 0.15. (h) FA shows newly developed CNV (arrow). (i) IA shows what are presumed to be newly developed polypoidal lesions (arrow).

Figure 4 Development of polypoidal lesions at the terminus of recently progressive choroidal neovascularization (CNV) in a right eye with typical age-related macular degeneration. (a) Fundus photograph at the initial visit shows atrophy of the retinal

pigment epithelium. Visual acuity was 0.4 in the right eye. (b) Fluorescein angiography (FA) at the initial visit shows subfoveal occult CNV. (c) Indocyanine green angiography (IA) shows CNV beneath the fovea, but no polypoidal lesions are seen. With photodynamic therapy, activity of the CNV regressed. (d) At 24 months after the initial visit, a new active lesion has developed at the temporal side of the regressed CNV. Visual acuity at this time was 0.4 in the right eye. (e) IA reveals multiple polypoidal lesions (arrows) at the edge of the progressive CNV. (f) Magnified IA shows that some of the polypoidal lesions consist of coiled vessels (arrow).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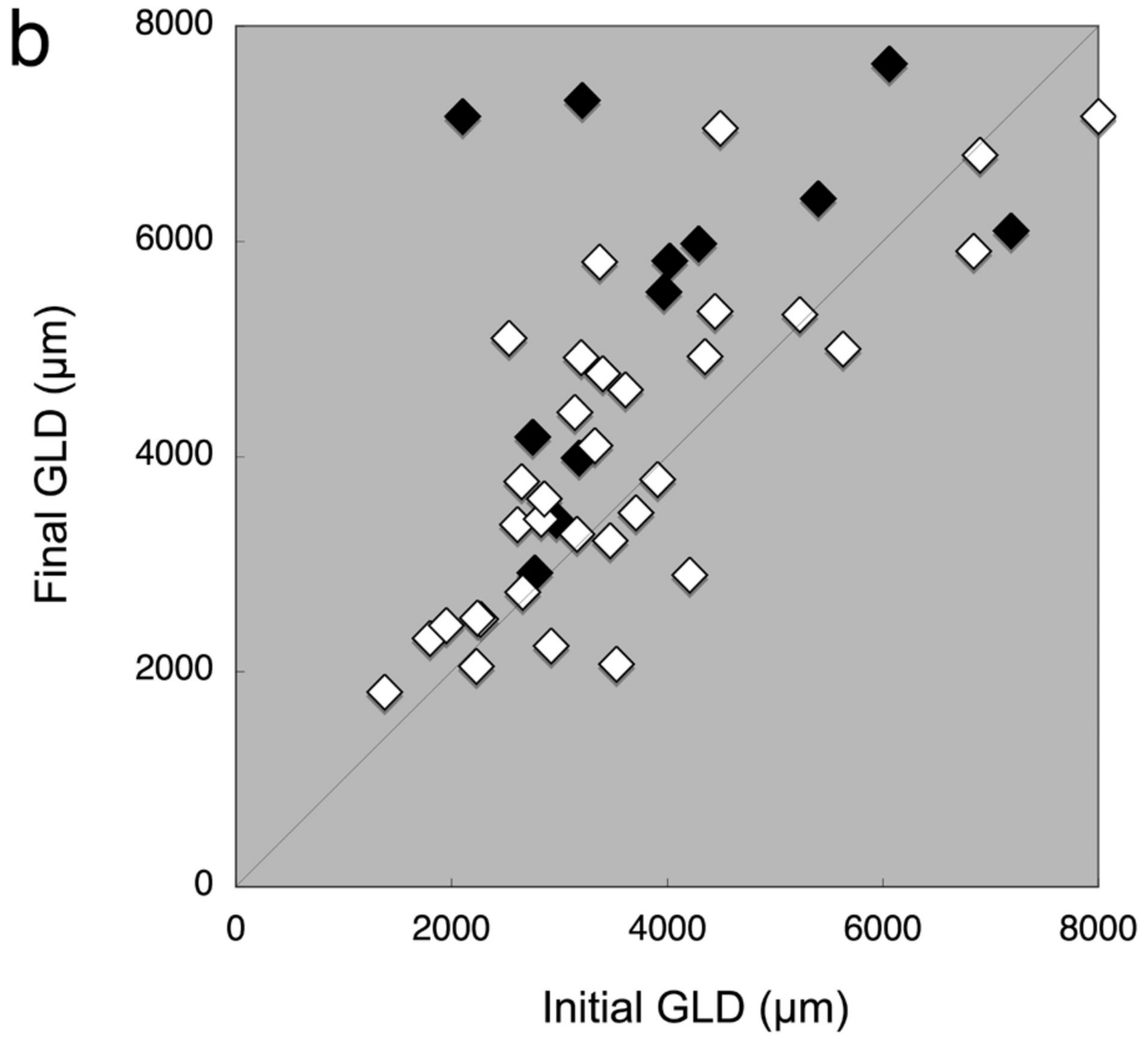
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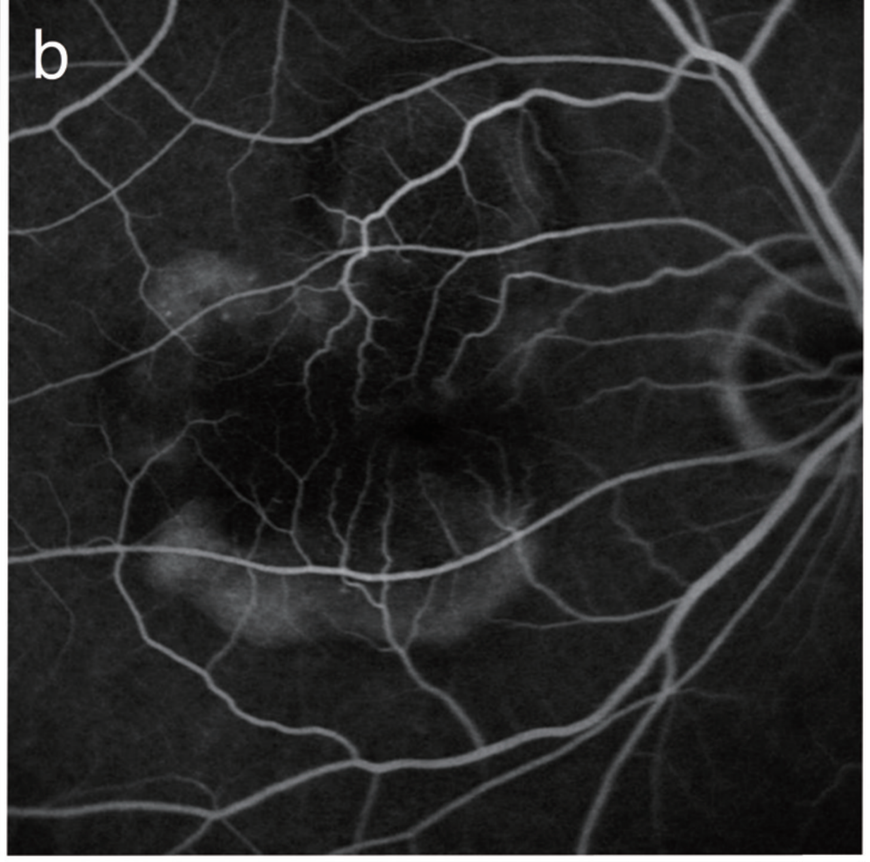
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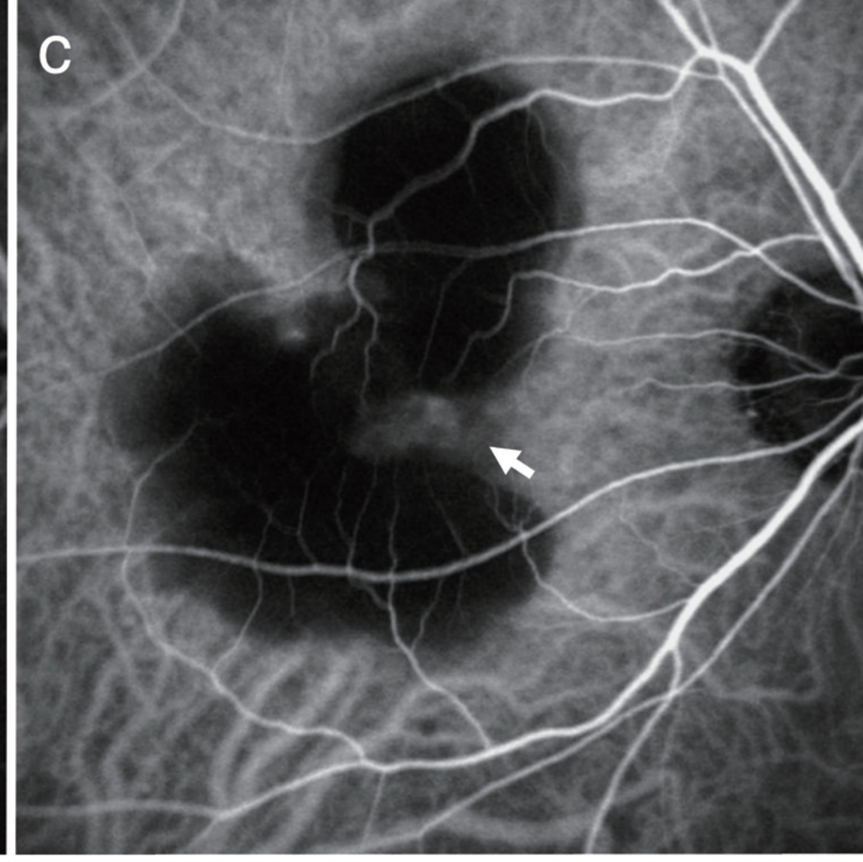
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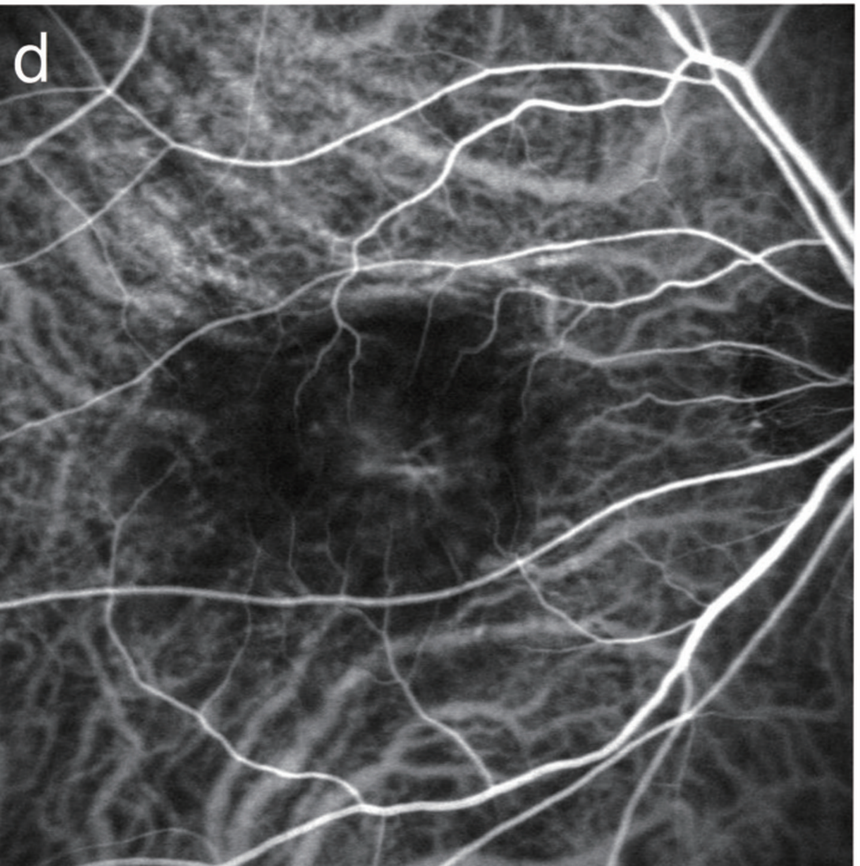
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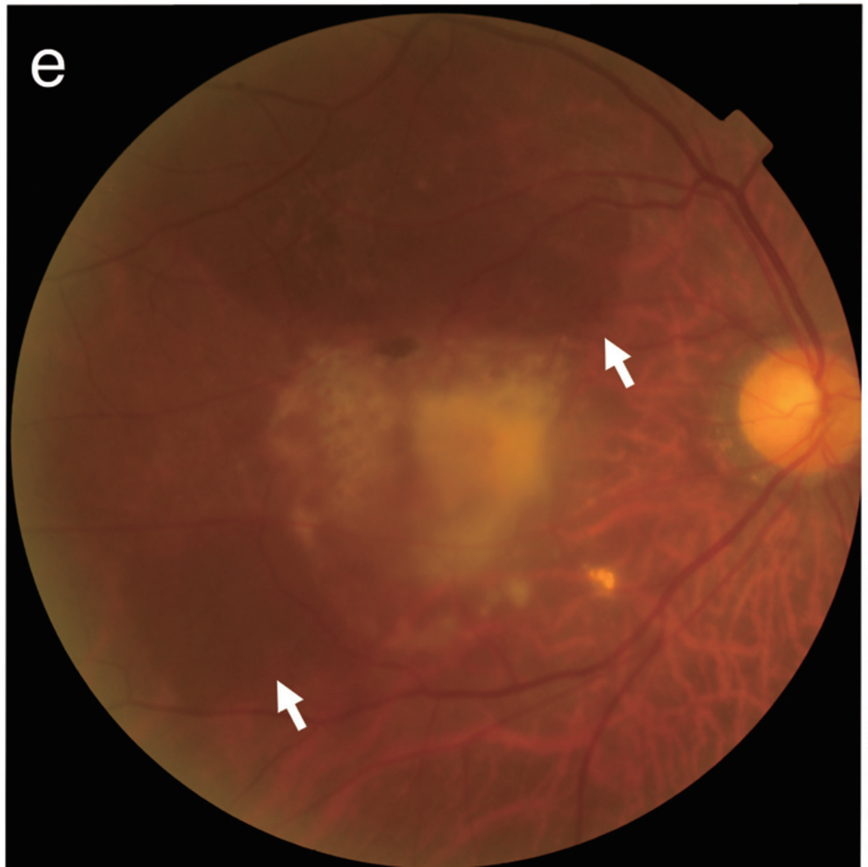
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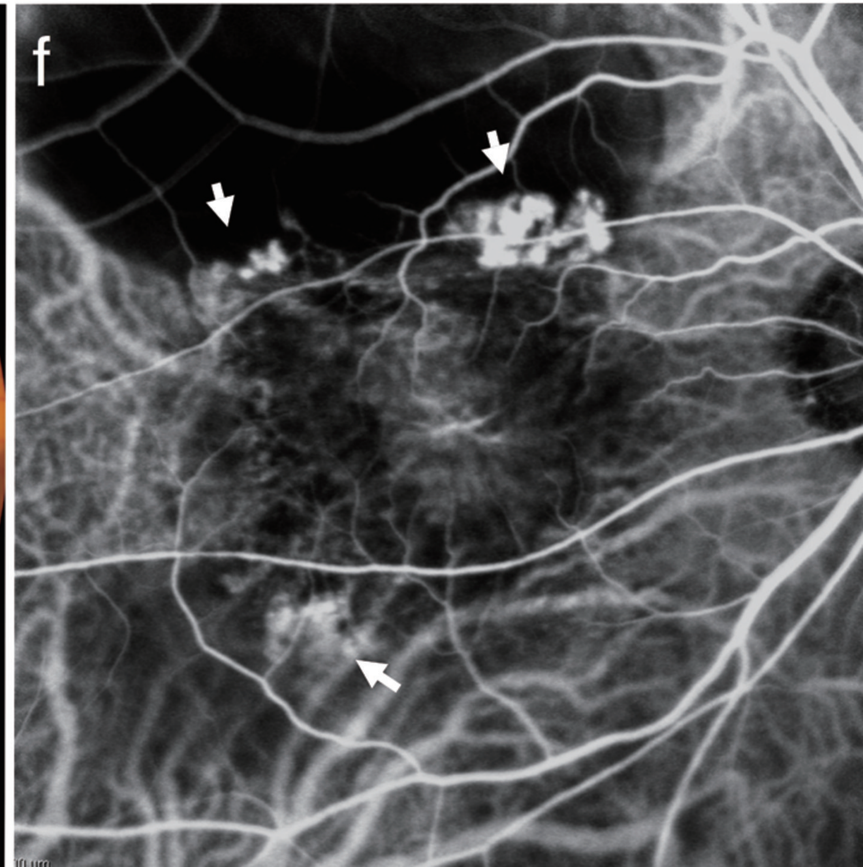
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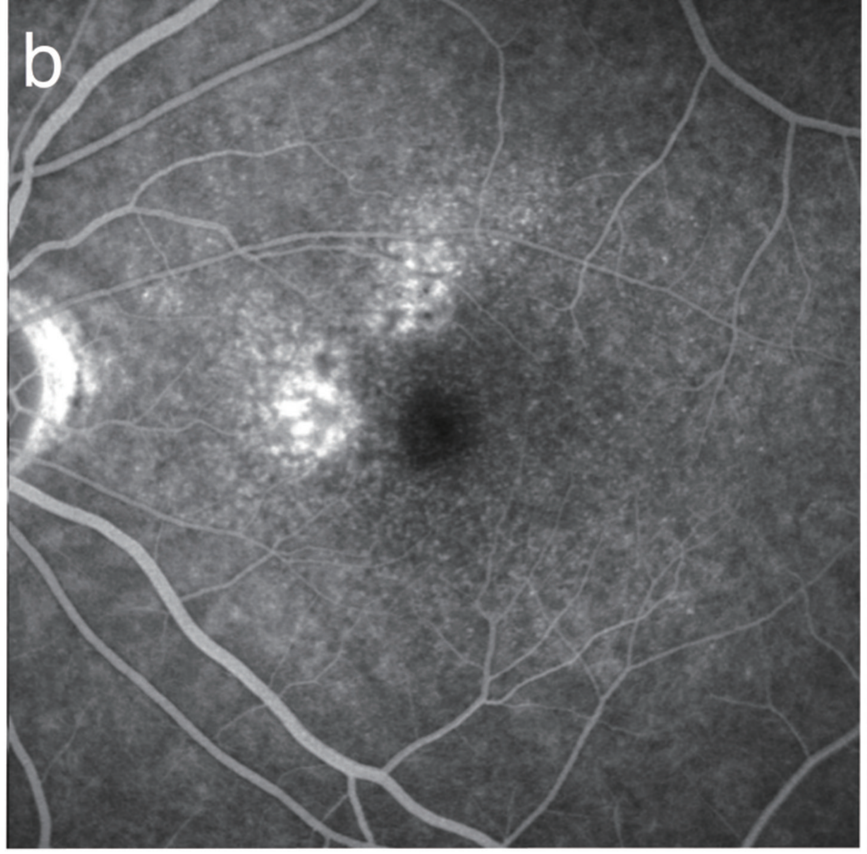
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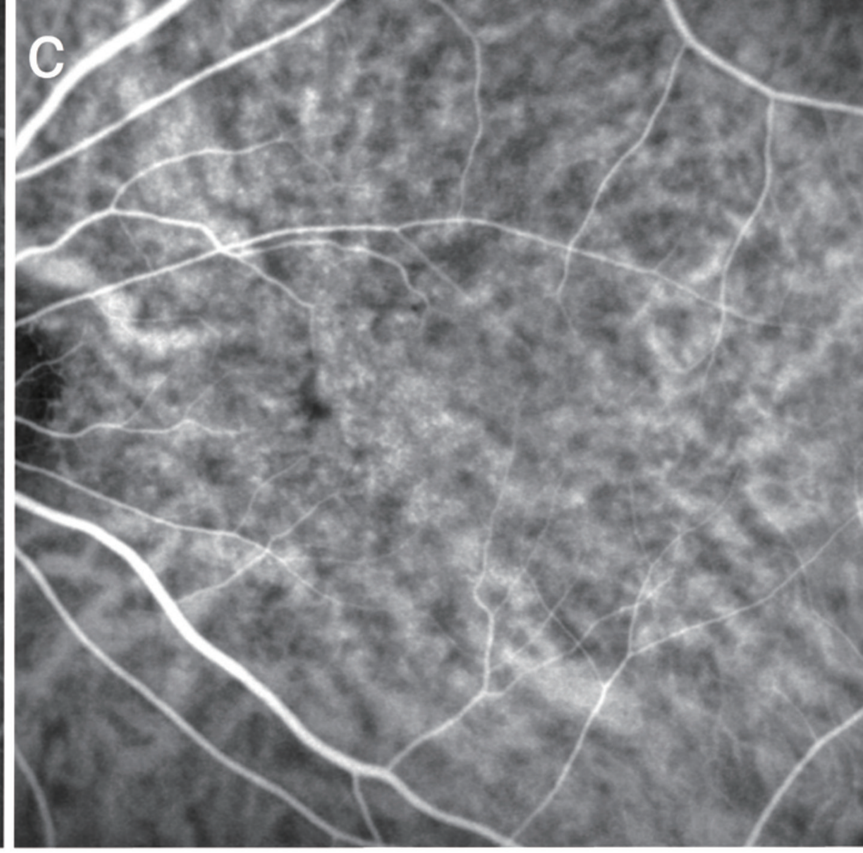
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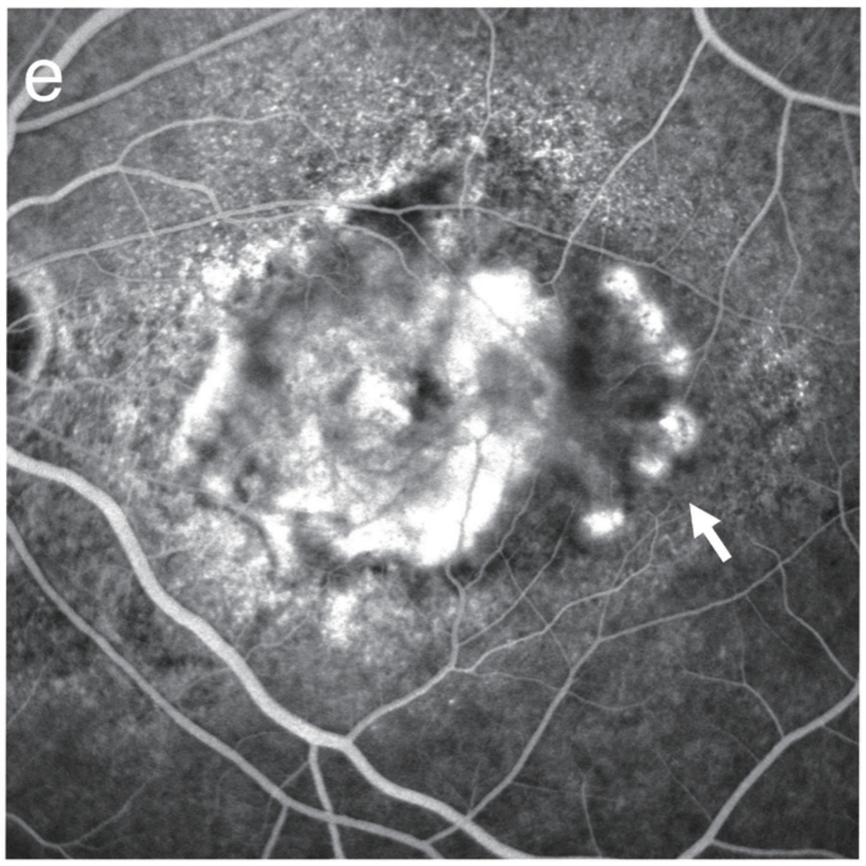
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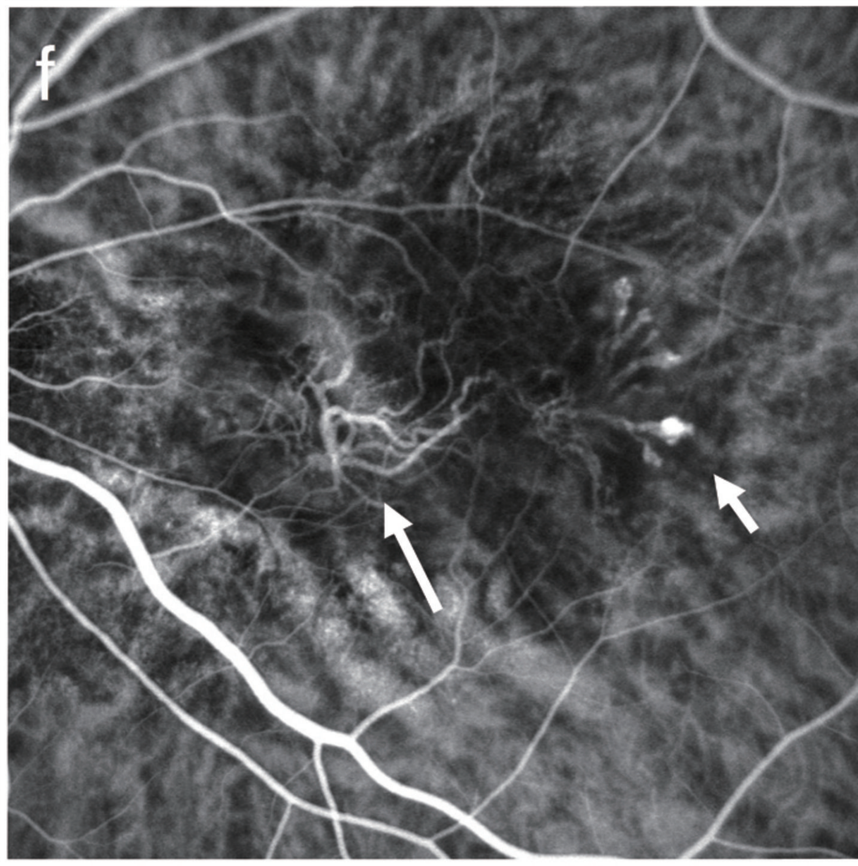
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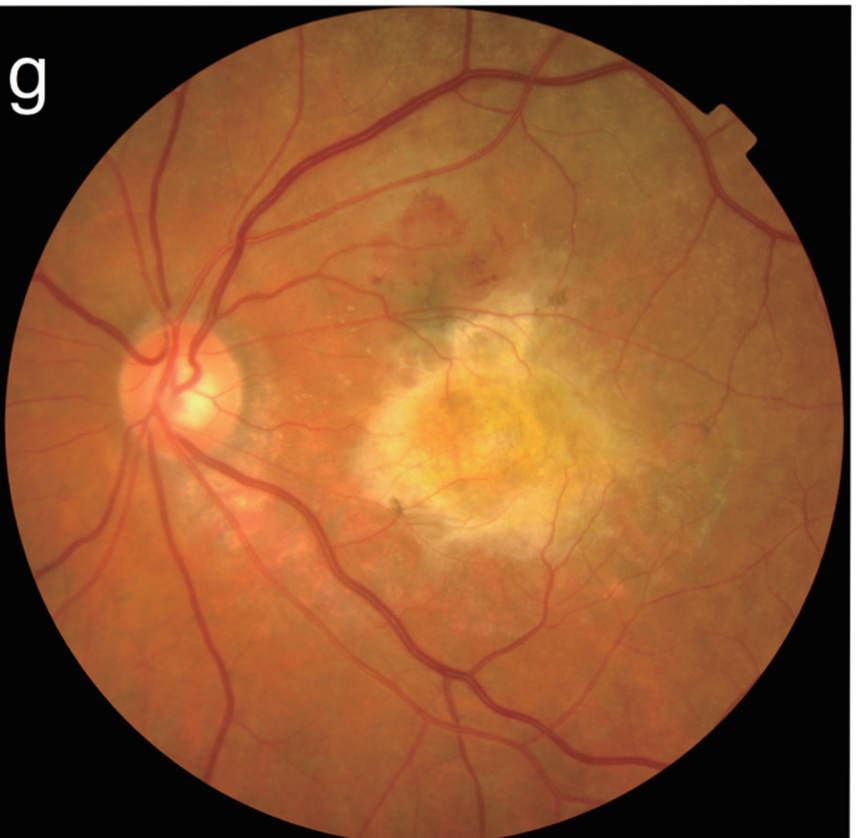
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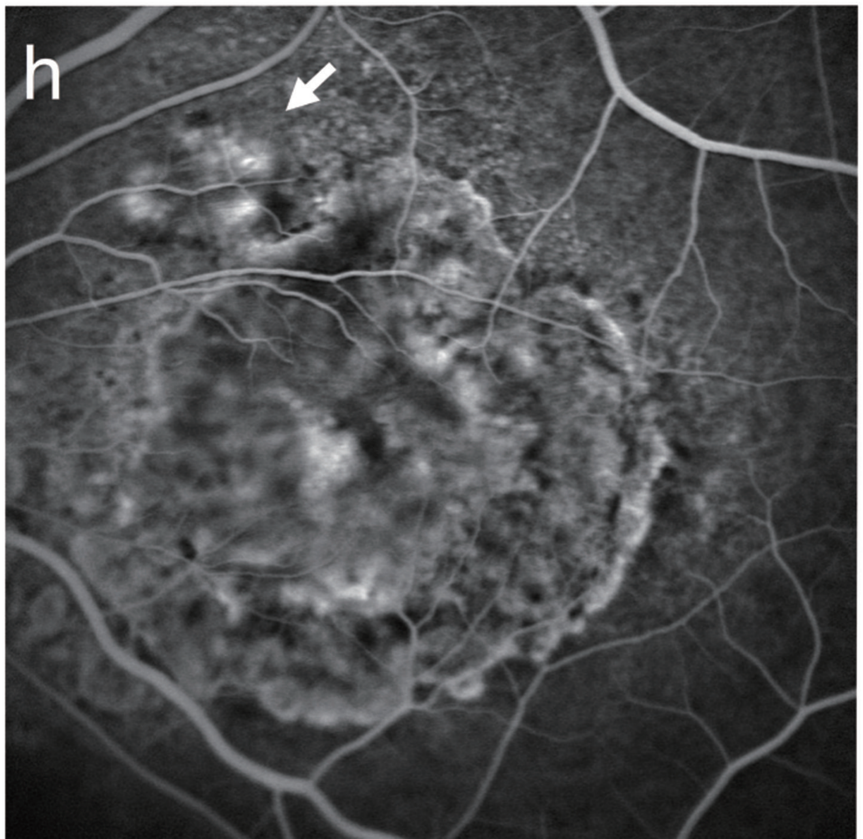
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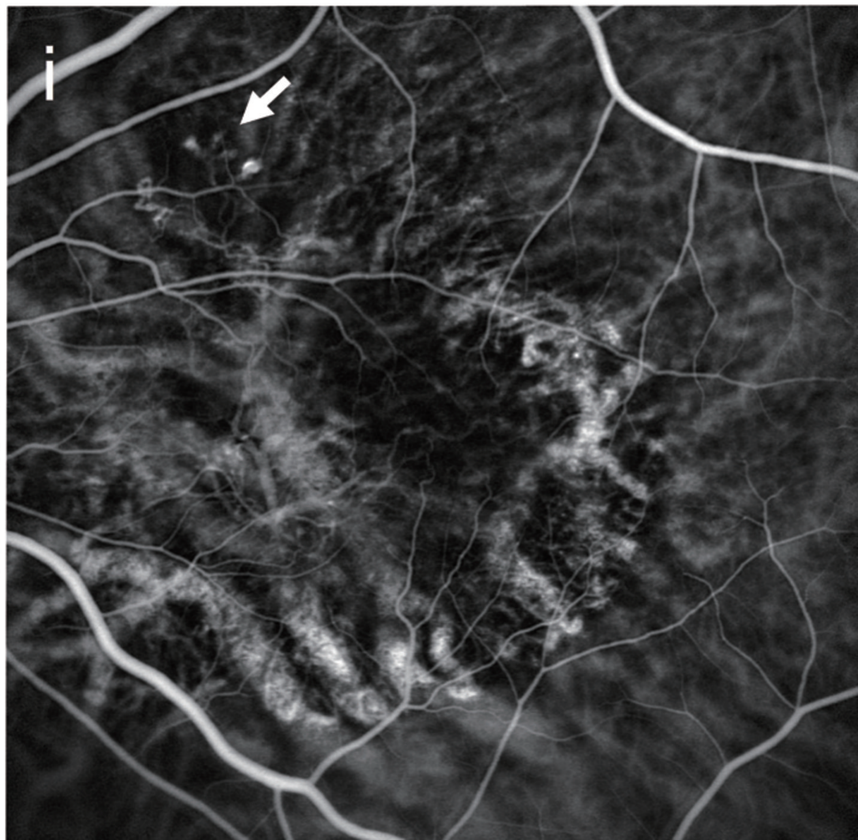
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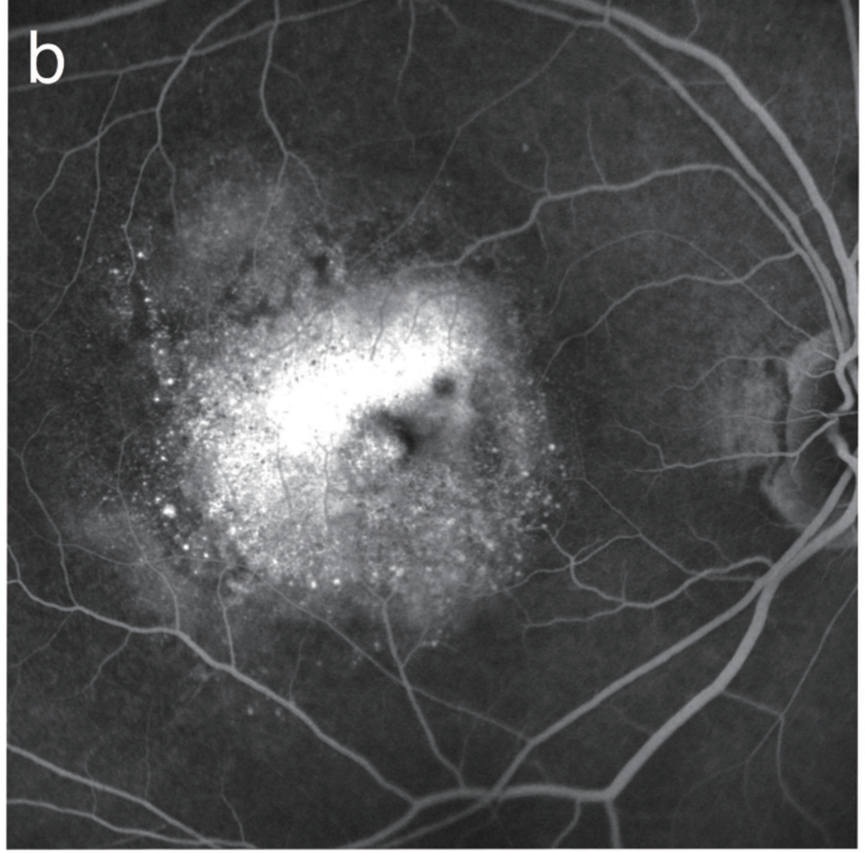
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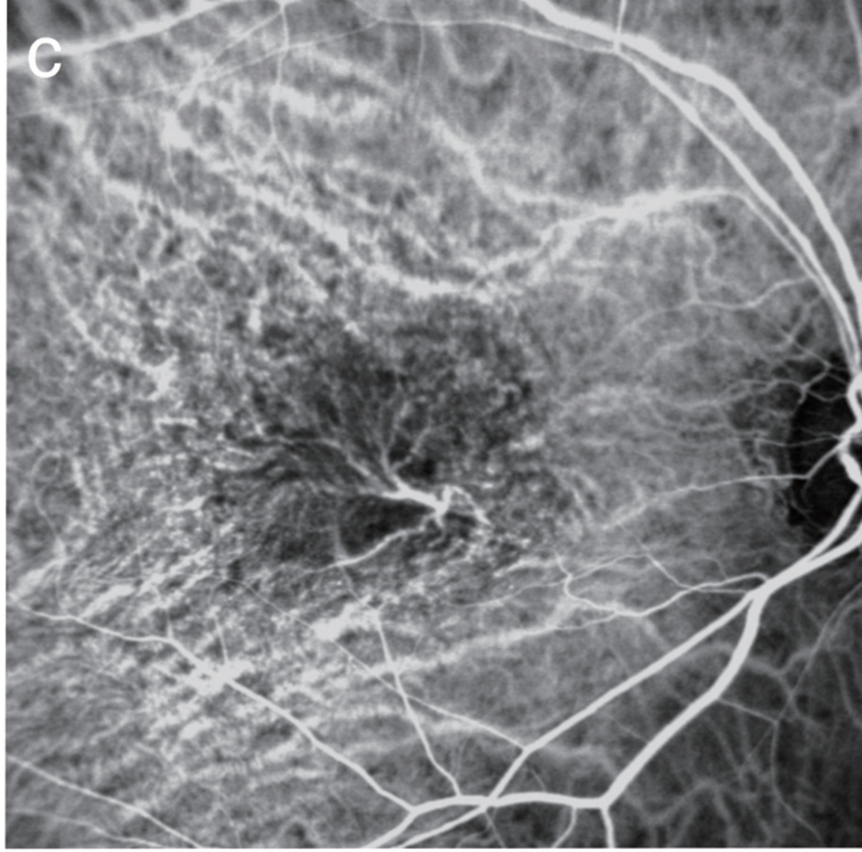
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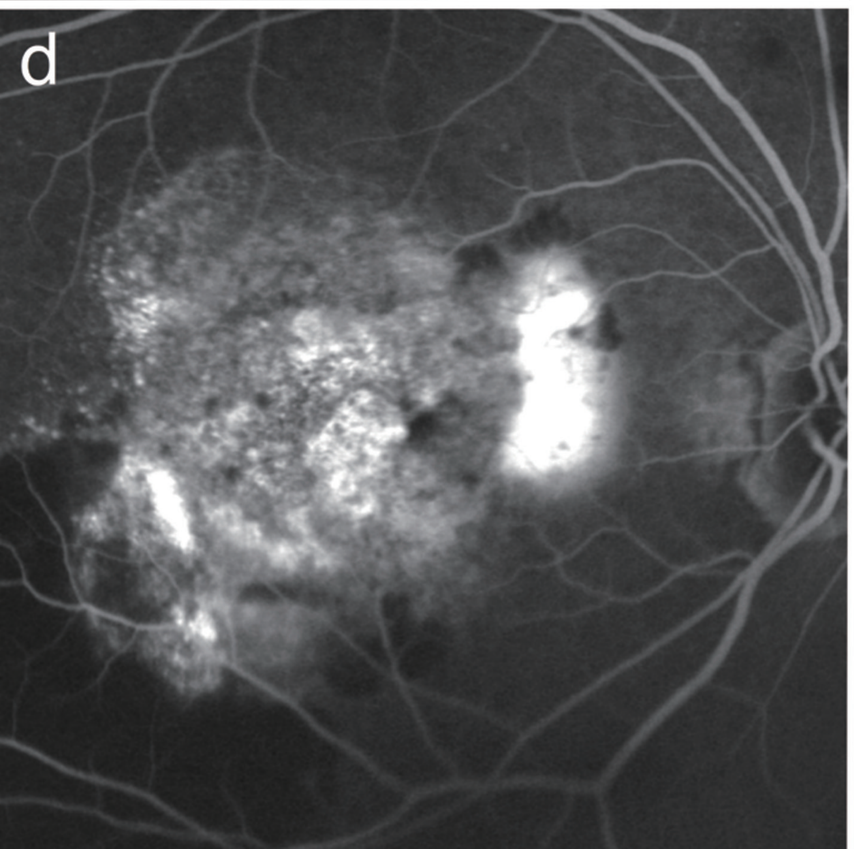
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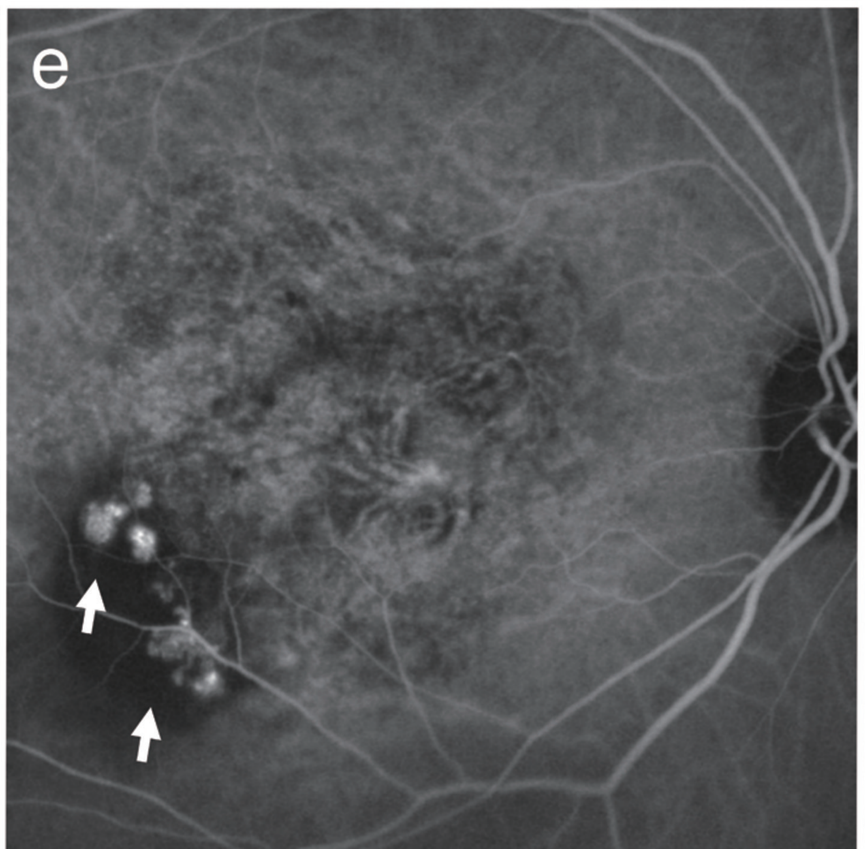
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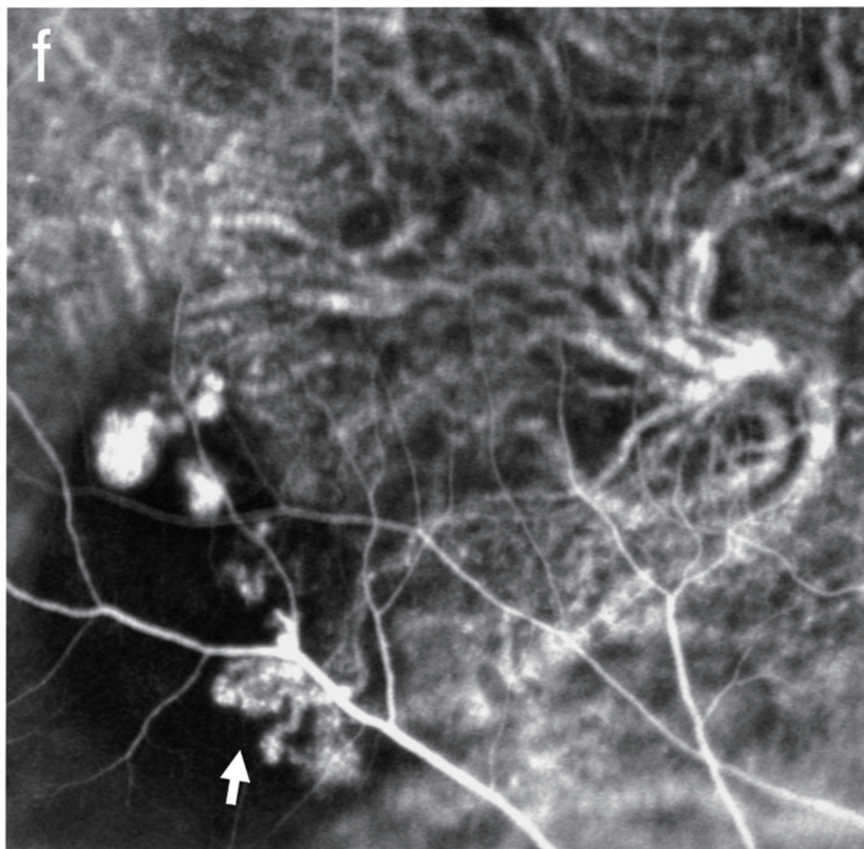
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Table 1 Characteristics of patients with typical age-related macular degeneration

	Total (n = 47)	Polypoidal lesion (+) (n = 13)	Polypoidal lesion (-) (n = 34)	*P* value
Gender (women/men)	11/36	3/10	8/26	0.9739
Age (years)	72.8 ± 7.5	73.1 ± 5.0	72.8 ± 7.5	0.8913
Initial conditions				
FA findings (predominantly classic/minimally classic/occult)	13/16/18	3/3/7	10/13/11	0.3857
Best-corrected VA (logMAR)	0.70 ± 0.53	0.64 ± 0.53	0.72 ± 0.53	0.6234
Area of lesion (mm^2)	8.68 ± 7.75	10.50 ± 7.88	7.99 ± 7.75	0.3262
GLD (μm)	3850 ± 1627	4231 ± 1692	3705 ± 1627	0.3269
Foveal thickness (μm)	523.8 ± 288.6	567.5 ± 427.9	507.1 ± 288.6	0.5269
Thickness of nerurosensory retina in the fovea (μm)	284.8 ± 199.5	314.2 ± 317.6	273.6 ± 199.5	0.5388
Follow-up duration (months)	43.9 ± 10.3	47.4 ± 9.1	42.5 ± 10.3	0.1481
Treatment				
Photodynamic therapy	35	8	27	0.2087
(number of treatments)	2.0 ± 1.1	2.4 ± 1.4	1.9 ± 1.1	0.3044
Anti-VEGF therapy	21	5	16	0.5959
(number of treatments)	3.1 ± 4.1	3.0 ± 2.9	3.2 ± 4.1	0.9322
Final conditions				
Best-corrected VA (logMAR)	0.89 ± 0.50	0.74 ± 0.40	0.94 ± 0.50	0.2303
Area of lesion (mm^2)	14.28 ± 10.57	20.87 ± 10.21	11.77 ± 10.57	0.0068
GLD (μm)	4628 ± 1893	5880 ± 1947	4149 ± 1893	0.0039
Foveal thickness (μm)	449.4 ± 352.8	467.7 ± 334.0	442.5 ± 352.8	0.8292
Thickness of nerurosensory retina in the fovea (μm)	245.0 ± 236.9	194.3 ± 127.6	264.4 ± 236.9	0.3700
Changes during follow-up				
Best-corrected VA (logMAR)	0.19 ± 0.45	0.11 ± 0.52	0.22 ± 0.45	0.4470
Area of lesion (mm^2)	5.60 ± 7.17	10.38 ± 9.35	3.78 ± 7.17	0.0036
GLD (μm)	777 ± 1306	1649 ± 1623	444 ± 1306	0.0035
Foveal thickness (μm)	-76.8 ± 364.6	-111.3 ± 463.5	-64.6 ± 364.6	0.7076
Thickness of nerurosensory retina in the fovea (μm)	-38.5 ± 284.7	-121.7 ± 328.1	-9.2 ± 284.7	0.2437

FA = fluorescein angiography; n = number; VA = visual acuity; logMAR=logarithm of the minimum angle of resolution; GLD = greatest linear dimension of the entire lesion; VEGF = vascular endothelial growth factor.